REMARKS

Claims 1-55 are currently pending in this application. Claims 1-11, 16, 17, 19, and 22-55 are withdrawn from consideration. Claims 13 and 15 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 12-15, 18, and 20-21 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and enablement. The Office also requires amendment to the specification to include sequence identifiers. By this reply, Applicant amends the specification and claims 12, 13, 15, 20-23, 25, 26, 29, 31-35, 37, 38, 41, 42, 44-46, 48, 49, 53, and 54, adds new claims 56 and 57, and addresses each of the objections and rejections below.

Support for the Amendment

Support for the amendment to claims 12, 20, 22, 23, 25, 32, 33, 34, 35, 37, and 48, and for new claims 56 and 57, is found on page 6, lines 8-25, and Example 2, pages 41-50, of the specification. Claims 13, 15, 26, 29, 31, 38, 41, 42, 44, 45, 46, 49, 53, and 54 are amended to correct typographical errors and to promote consistency between the claims.

In addition, Applicant has amended the specification to include sequence identifiers for the sequences shown in Figures 2 and 3. Finally, Applicant has amended page 17 of the specification to remove a typographical error (duplication).

No new matter is added by the amendment.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Office states that claim 13 "is unclear and indefinite since it recites myasthenia gravis as the autoimmune disease twice" (Office Action, p. 2). Applicant has amended claim 13 to correct this typographical error. This rejection can now be withdrawn.

Claim 15 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Office states that "[c]laim 15 is indefinite in the recitation of FasL, TNF, IL1, IL-6, IL-12, and IFN-gamma as being 'chemokines'...None of the recited molecules in claim 15 are chemokines" (Office Action, p. 2). Applicant has amended claim 15 to remove the term "chemokines." This

rejection can now be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Written Description

The Office rejects claims 12-15, 18, and 20-21 under 35 U.S.C. § 112, first paragraph, for lack of written description, stating that "there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of 'compounds' that decrease the viability of leukocytes and 'TNF-alpha receptor agonists'" (Office Action, p. 3). Applicant respectfully disagrees, but, in an effort to expedite prosecution of pending claims 12-15, 18, 20, 21, 56, and 57, Applicant has amended present independent claim 12 to replace the term "compound" with the phrase a "composition comprising a TNF-alpha inducing substance, a TNF-alpha agonist, or TNF-alpha." The present specification provides an ample written description of TNF-alpha inducing substances and TNF-alpha agonists, including TNF-alpha, sufficient to reasonably convey to one skilled in the art at the time of the invention that Applicant was in possession of the invention of present claims 12-15, 18, 20, 21, 56, and 57 (see, e.g., page 6, line 8, through page 7, line 19, of the present specification). Applicants respectfully request that the rejection of claims 12-15, 18, and 20-21 can now be withdrawn.

Enablement

The Office also rejects claims 12-15, 18, and 20-21 under 35 U.S.C. § 112, first paragraph, for lack of enablement, stating that "the specification provides insufficient evidence that the claimed method would function to diagnose autoimmune disease as broadly claimed" (Office Action, p. 4). Applicant respectfully disagrees.

The M.P.E.P. § 2164.01(b) states that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." Applicant has plainly met this standard.

Independent claim 12, as presently amended, is directed to a method for diagnosing an

autoimmune disease, or a predisposition to develop autoimmune disease, in a mammal. The method involves determining the presence of, or the predisposition to develop, an autoimmune disease by measuring a decrease in the viability of leukocytes within a first blood sample from a mammal to be tested following exposure of the sample to a composition that includes a TNF-alpha inducing substance, a TNF-alpha agonist, or TNF-alpha. Leukocyte viability in the sample is then compared to the viability of leukocytes in a second blood sample (e.g., from a healthy mammal) that has also been contacted with the composition.

The invention of present independent claim 12, and claims dependent therefrom, is based, at least in part, on Applicant's discovery that autoreactive immune cells (leukocytes) present in mammals having or predisposed to having autoimmune disease are killed by exposure to TNF-α inducers or agonists (see, e.g., page 18, lines 4-18; page 19, lines 3-22; and Example 1, pages 37-41), whereas immune cells from healthy mammals are more resistant to cell killing upon exposure to TNF-α inducers or agonists. Applicant recognized that this differential response to TNF-α, TNF-α inducing substances, or TNF-α agonists could be used to diagnose autoimmune disease in a mammal, such as a human, or the predisposition of a mammal to develop autoimmune disease.

Present independent claim 12, and claims dependent therefrom, plainly satisfy the enablement requirement of 35 U.S.C. § 112, because Applicant's specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of present claims 12-15, 18, and 20-21 (M.P.E.P. § 2164.01(b)). Specifically, Applicant's specification teaches that contacting leukocytes from NOD mice, which is an accepted animal model of type 1 (autoimmune) diabetes mellitus, Sjogren's syndrome, and lupus in humans, with TNF-α or a TNF-α inducing agent, in particular BCG, results in the preferential cell killing of autoreactive leukocytes (see, e.g., page 18, lines 4-18; and page 57, line 6, through page 60, line 9), as determined using one or more of the cell viability assays described in the present specification (e.g., page 27, lines 14-26; and page 35, lines 10-17) or known in the art. The specification also teaches the application of the methods of the invention in the diagnosis of autoimmune disease in humans. In particular, the specification demonstrates that human peripheral blood lymphocytes from human diabetics exhibit increased sensitivity to TNF-α

relative to control subjects (see page 41, line 20, through page 46, line 22). Thus, the present specification clearly provides evidence that the diagnostic methods of the present invention are fully enabled because TNF-α, TNF-α inducing substances, and TNF-α agonists selectively eliminate autoreactive immune cells in mammals having autoimmune diseases or predisposed to develop autoimmune disease. Accordingly, the specification clearly teaches, and provides experimental evidence that confirms, that several, disparate autoimmune diseases can be diagnosed by contacting autoreactive immune cells from patients (e.g., a human) having or predisposed to have autoimmune disease with a TNF-α inducer or agonist, such as TNF-α, a TNF receptor agonist, or other TNF-α inducing substance (such as BCG or CFA), because these agents preferentially promote autoreactive immune cell death. Thus, Applicant submits that the full scope of present claims 12-15, 18, 20-21, and 56-57 is enabled.

As further evidence that the full scope of the method of present claims 12-15, 18, 20-21, and 56-57 is enabled, Applicant directs the Office to the enclosed Declaration of the inventor, Dr. Denise Faustman, who states that her data show that several, disparate autoimmune diseases can be diagnosed according to the methods of present claims 12-15, 18, 20-21, and 56-57 by contacting a TNF-α inducer or agonist, such as TNF-α, a TNF receptor agonist, or other TNF-α inducing substance (such as BCG or CFA), to a sample of cells containing leukocytes from a mammal (e.g., a human) (see ¶¶ 4 and 5 of the Declaration). Dr. Faustman states that autoreactive immune cells responsible for development of autoimmune diseases are sensitive to exposure to TNF-α and TNF-α inducers (e.g., agonists), which induce death in these cells, owing to a genetic defect in the NF-κB signaling pathway (see ¶ 4 of the Declaration). In addition, Dr. Faustman states that she has conducted additional experiments, which are described in the present declaration, that support and further validate the data reported in the present specification; these data provide clear evidence that autoreactive immune cells from NOD mice and human autoimmune patients are sensitive to exposure to TNF-α and TNF-α inducers (e.g., agonists), which induce death in these cells (see ¶ 5 of the Declaration).

In addition, at ¶ 6 of the Declaration, Dr. Faustman states that researchers working under her direction have shown that autoreactive immune cells obtained from human patients having several disparate autoimmune diseases, including, e.g, Type 1 diabetes, lupus, scleroderma,

Sjogren's syndrome, hypothyroidism, multiple sclerosis, Crohn's disease, and psoriasis, undergo cell death when exposed to TNF-α agonists, such as TNF-α (see Exhibit A). Dr. Faustman also states that she has observed TNF-α-agonist-induced autoreactive immune cell death in samples from over 1000 type 1 diabetics studied, and in her studies of 50 patients with lupus, 8 patients with scleroderma, 8 patients with Sjogren's syndrome, 50 patients with hypothyroidism, 20 patients with multiple sclerosis, 15 patients with Crohn's disease, and 6 patients with psoriasis (see ¶ 6 of the Declaration). Furthermore, Dr. Faustman states that her results confirm that autoreactive immune cells can be distinguished from normal cells not only by defects in NF-kB signaling on a molecular level, but also on a cellular level by targeted cell death via TNF-α agonism, which is a symptom of the NF-kB interruption (see ¶ 6 of the Declaration).

In ¶¶ 7 and 8 of the Declaration, Dr. Faustman reports that, in addition to TNF-α, other TNF-α agonists promote autoreactive immune cell death. In particular, Dr. Faustman states that she has observed that TNF-α agonist antibodies promote cell death in autoreactive immune cells from human patients having diabetes, lupus, multiple sclerosis, psoriasis, Crohn's and rheumatoid arthritis (see Exhibit B), while other substances, such as BCG, which induce endogenous TNF-α expression, promote the death of autoreactive immune cells from NOD mice.

The data presented in the Declaration of Dr. Faustman clearly demonstrate that TNF-inducer substances, including, e .g., TNF-α agonists, such as TNF-α, TNF-α agonist antibodies, and BCG, promote the death of autoreactive immune cells isolated from a mammal, e.g., a human, having or predisposed to develop autoimmune disease, but not immune cells from normal mammals. Thus, Dr. Faustman's data confirm that the method of present claims 12-15, 18, 20-21, and 56-57, can be used to diagnose autoimmune disease (or a predisposition to develop autoimmune disease) by measuring the viability of leukocytes obtained from a mammal to be tested following their contact with one or more of these substances, and determining whether there is a decrease in cell viability relative to a second, control sample containing leukocytes (e.g., from a normal mammal), which indicates the presence of autoimmune disease (or predisposition to develop autoimmune disease). Accordingly, Dr. Faustman's additional data further demonstrate that the full scope of the method of present claims 12-15, 18, 20-21, and 56-57 is predictable and enabled.

Summary

In summary, the data in the present specification and the accompanying Declaration of Dr. Faustman confirms that the method of present claims 12-15, 18, 20-21, and 56-57 can be performed successfully to diagnose autoimmune disease or a predisposition to develop autoimmune disease in a mammal without undue experimentation. For this reason, Applicant respectfully requests that the rejection of claims 12-15, 18, and 20-21 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

CONCLUSION

In view of the above remarks, Applicant respectfully submits that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including September 13, 2007, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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